REMARKS

Reconsideration is requested.

Claims 31-63 have been canceled, without prejudice. Claims 64-86 have been added and are pending. Claims 64-78 correspond, in part, to canceled claims 31, 33-41, 49 and 51-54, respectively. Claim 64 includes the details of canceled claims 31 and 32. Claims 64 provides a further variant of the disclosed invention. New claim 65 is directed to a method of inducing DNA synthesis using the HGF variant of the disclosed invention. New claim 81 provides a method of inducing dissociation and scattering of cells in a cell population using an HGF variant of the disclosed invention. DNA synthesis and cell dissociation and the scattering are consequences of HGF binding to its receptor. See, Figures 4, 5 and 6 of the present application as well as the discussion on page 41, line 23 to page 42, line 4 of the specification. No new matter has been added.

The Examiner is requested to acknowledge the claim for foreign priority and receipt of the certified copies of the priority document in the Examiner's next Action. See, the Patent Office Notification dated March 3, 2000.

Clarification is requested with regard to the Examiner's objection of the Sequence Listing stated on page 3 of the Office Action dated June 27, 2002 (Paper No. 18) as the indicated page 3, line 7 of the specification is not believed to contain a nucleic acid or amino acid sequence which would be required to be included in the Sequence Listing or identified as already having been included in the Sequence Listing. Clarification is requested in this regard. The applicants believe the amendments to the specification filed

with the Amendment of July 27, 2001, was complete in this regard however the Examiner is requested to contact the undersigned if anything further is required.

The Section 101 rejection of claims 31-41 and 49-54 is moot. The pending claims define patentable subject matter. The Examiner is requested to identify any naturally occurring HGF which may be defined by the present claims. The applicants note in this regard that page 3, lines 10-19 in the specification defines a variant HGF as HGF which differs in primary amino acid sequence from the wild-type form. The wild-type form is defined as including naturally occurring sequence variation of HGF, provided that such HGF binds heparin sulphate proteoglycan, it binds the HGF receptor, and gives rise to the known biological effect of HGF.

Thus, as defined in the specification and the claims, a variant HGF is not a naturally occurring HGF polypeptide and it does not "encompass all naturally occurring polypeptides comprising HGF related proteins, thereby not involving the hand of man to isolate or purify the polypeptide", as stated by the Examiner.

Moreover, the insertion of the term "polypeptide" is not believed to be required, as suggested by the Examiner. See, page 3 of Paper No. 18. One of ordinary skill in the art will appreciate that HGF is a polypeptide and the inclusion of such a recitation should not be required to define patentable subject matter.

The Section 112, first paragraph, rejection of claims 31-21 and 49-50 stated on page 4 of Paper No. 18 is moot. The claims are supported by an adequate written description.

As admitted by the Examiner, the present specification describes a "human HGF molecule" (see, page 4 of Paper No. 18), as presently claimed. The term human HGF also includes HGF molecules with naturally occurring sequence variation from the human HGF sequence of Figure 7 however. See, page 3, lines 13-19 of the specification. The presently claimed invention requires such a variant to bind heparin sulfphate proteoglycan and bind the HGF receptor. Moreover, the claimed variant possesses the known biological effect of HGF. The Examiner is urged to appreciate that new claims 64 and 74 are not directed to any variant of human HGF, but to a variant of human HGF wherein a positively charged amino acid residue in the hairpin loop structure of wild-type human HGF has been replaced with an amino acid residue with a negative charge. Accordingly, the claimed invention relates to human HGF with a sequence, such as exemplified in Figure 7, or to a naturally occurring variant of the sequence in which the further specified mutation has been provided. The applicants submit that one of ordinary skill in the art would appreciate from the specification that the applicants were in possession of the invention at the time the application was filed. The application is believed to adequately describe the presently claimed invention.

The Section 112, first paragraph, rejection of claims 31-41 and 49-54 stated on pages 4-6 of Paper No. 18 is moot in view of the above. The specification is believed to enable one of ordinary skill in the art to practice the presently claimed invention.

The applicants urge the Examiner to appreciate that the presently claimed invention provides a variant human HGF in which a positively charged amino acid residue in the hairpin loop structure has been replaced with an amino acid residue with a

negative charge. This exactly defines which residues are critical and a variant HGF which is incapable of binding a heparin sulfate proteoglycan but which binds to the HGF receptor.

Page 6, lines 12 to 13 of the specification teach that the hairpin loop structure of human HGF spans amino residues 70 to 96. Page 7 line 30 and page 8 line 1 further teach that in wild-type human HGF the positively charged amino acid residues in the hairpin loop structure include R73, R76, K78, K85, K91, R93 and K94. Thus the invention requires that at least one of seven specified positively charged amino acid residues is changed to a negatively charged amino acid residue. This is a clear structural characteristic of the invention. As the Examiner stated that the specification is enabling for claims to structurally characterized HGF variants, the applicants believe that the presently claimed invention is supported by an enabling disclosure.

The Section 112, second paragraph, rejections stated in paragraphs 5-7 of Paper No. 18 are moot in view of the above. The claims are submitted to be definite. The claims have been amended with the Examiner's helpful comments in mind.

The Section 102 rejection of claims 31-32 and 34 over Sakata and the Section 102 rejection of claims 31-32 and 34 over Lokker are moot in view of the above. The presently claimed invention is submitted to be patentable over the cited art and consideration of the following in this regard is requested.

As correctly noted by the Examiner, each of the cited documents disclosure HGF molecules in which a positively charged amino acid residue of the hairpin loop structure has been changed to alanine, which is a neutral, uncharged, amino acid. The cited art

does not teach or suggest replacing positively charge residues in the hairpin loop structure with a negatively charged residue. Accordingly, as the cited art fails to teach each and every aspect of the presently claimed invention, the claims are submitted to be patentable over the cited art.

The Examiner's objection to the Declaration on page 9 of Paper No. 18 is noted and the Examiner is requested to hold the objection in obeyance. The revised or a substitute Declaration will be forwarded under separate cover once received by the undersigned.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:plb
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100